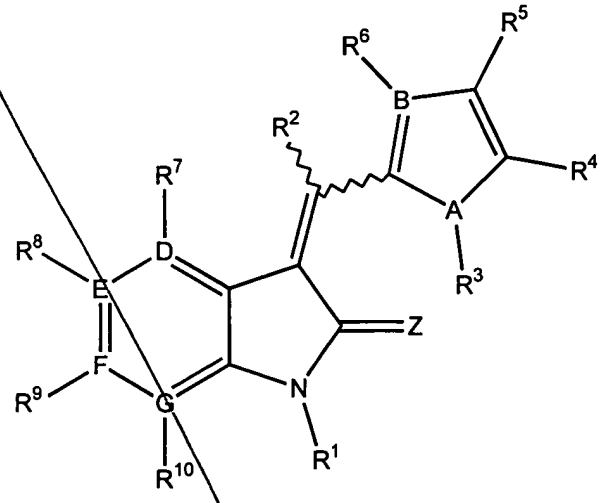
CLAIMS

WHAT IS CLAIMED IS:

1. A 3-heteroarylideneazaindolin-2-one compound having the following chemical structure:



wherein,

A is selected from the group consisting of nitrogen, oxygen and sulfur and it is understood that when A is oxygen or sulfur, R^3 does not exist and there is no bond;

B, D, E, F and G are independently selected from the group consisting of carbon and nitrogen but at least one of D, E, F and G must be nitrogen and it is understood that when B, D, E, F or G is nitrogen, R^6, R^7, R^8, R^9 and R^{10}, respectively, do not exist and there is no bond;

Z is selected from the group consisting of oxygen, sulfur and NR^{11} wherein,

R^{11} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and

trihalomethanesulfonyl;

R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, trihalomethanecarbonyl, sulfonyl, trihalomethanesulfonyl, C-carboxyl, O-carboxyl, C-amido, and guanyl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and halogen;

when A is nitrogen,

R^3 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl;

R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino and $-NR^{12}R^{13}$, wherein

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

R^4 and R^5 or R^5 and R^6 may combine to form a six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring;

and the physiologically acceptable salt and prodrugs thereof.

2. The compound, salt or prodrug of claim 1 wherein R^1 is selected from the group consisting of hydrogen and alkyl.

3. The compound, salt or prodrug of claim 2 wherein Z is oxygen.

4. The compound, salt or prodrug of claim 3 wherein R^2 is hydrogen.

5. The compound, salt or prodrug of claim 4 wherein R^7, R^8, R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, alkoxy, thioalkoxy, nitro, amino and N-amido.

6. The compound, salt or prodrug of claim 5 wherein D is nitrogen.

7. The compound, salt or prodrug of claim 5 wherein E is nitrogen.

8. The compound, salt or prodrug of claim 5 wherein F is nitrogen.

9. The compound, salt or prodrug of claim 5 wherein G is nitrogen.

10. The compound, salt or prodrug of claim 5 wherein E and G are nitrogen.

11. The compound, salt or prodrug of claim 1 wherein A is nitrogen.

12. The compound, salt or prodrug of claim 11 wherein R^3

contd. C4 is selected from the group consisting of hydrogen and alkyl.

13. The compound, salt or prodrug of claim 12 wherein R^4, R^5 and R^6 are independently selected from the groups consisting of hydrogen, alkyl, C-carboxy and a six-member cycloalkyl ring formed by the combination of R^4 and R^5.

14. The compound, salt or prodrug of claim 12 wherein R^4 and R^6 are alkyl and R^5 is hydrogen.

15. The compound, salt or prodrug of claim 1 wherein A is sulfur.

16. The compound, salt or prodrug of claim 15 wherein R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkynyl, aryl, heteroaryl, aryloxy, thioalkoxy, halo, nitro, trihalomethane-carbonyl and an aryl ring or a heteroaryl ring formed by the combination of R^4 and R^5.

17. A compound selected from the compounds shown in Table 1.

18. A compound selected from the group consisting of 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, 3-(3,5-diethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, 3-(3H-imidazol-4-ylmethylene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, 3-[4-methyl-5-(2-oxo-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid, and 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid.

Amen. C5 ~~19. A pharmacological composition of said compound, salt or prodrug of any one of claims 1-18.~~

contd. C5

20. A method for the modulation of the catalytic activity of a protein tyrosine kinase comprising administering said compound, salt of prodrug of any one of claims 1-18 to said protein tyrosine kinase.

21. A method for treating or preventing a protein tyrosine kinase related disorder in an organism comprising administering a therapeutically effective amount of said pharmacological composition of claim 19 to said organism.

22. The method of claim 21 wherein said protein tyrosine kinase related disorder comprises a cell proliferation, differentiation or growth disorder.

23. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a PDGF related disorder.

24. The method of claim 23 wherein said PDGF related disorder comprises cancer.

25. The method of claim 24 wherein said cancer comprises blastoglioma, Kaposi's sarcoma, melanoma, lung cancer, ovarian cancer or prostate cancer.

26. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a EGF related disorder.

27. The method of claim 26 wherein said EGF related disorder comprises cancer.

28. The method of claim 27 wherein said cancer comprises squamous cell carcinoma, astrocytoma, glioblastoma, head and

neck cancer, lung cancer and bladder cancer.

29. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a IGF related disorder.

30. The method of claim 29 wherein said IGF related disorder comprise cancer.

31. The method of claim 30 wherein said cancer comprises breast cancer, small-cell lung cancer, and gliomas.

32. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a met related disorder.

33. The method of claim 32 wherein said met related disorder comprises cancer.

34. The method of claim 33 wherein said cancer comprises colorectal cancer, thyroid cancer, pancreatic and gastric carcinoma, leukemia and lymphoma, Hodgkin's disease and Burkitts disease.

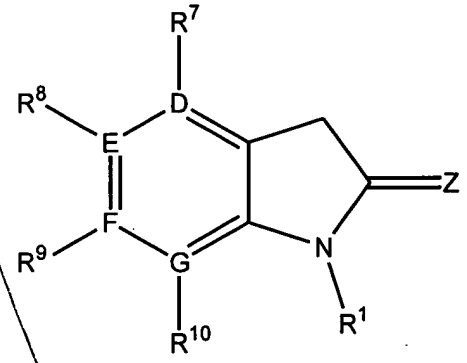
35. The method of claim 21 wherein protein tyrosine kinase related disorder comprises arthritis, diabetic retinopathy, restinosis, hepatic cirrhosis, atherosclerosis, angiogenesis, glomerulonephritis, diabetic nephropathy, thrombic microangiopathy syndromes, transplant rejection, autoimmune disease, diabetes or hyperimmune disorders.

36. The method of claim 21 wherein said organism is a mammal.

37. The method of claim 36 wherein said mammal is a

human.

38. A combinatorial library of at least 10 3-heteroarylideneazaindolin-2-one compounds that can be formed by reacting an azaindolin-2-one with an acyl compound, wherein said azaindolin-2-one has a structure set forth in formula 2

(2) 

wherein

D, E, F and G are independently selected from the group consisting of carbon and nitrogen but at least one of D, E, F and G must be nitrogen and it is understood that when D, E, F or G is nitrogen, R^7, R^8, R^9 and R^{10}, respectively, do not exist and there is no bond;

R^7, R^8, R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino, and $-NR^{12}R^{13}$, wherein

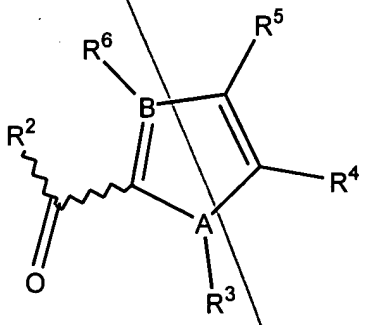
R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

Z is selected from the group consisting of oxygen, sulfur and NR^{11} wherein,

R^{11} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl; and

R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, trihalomethanecarbonyl, sulfonyl, trihalomethanesulfonyl, C-carboxyl, O-carboxyl, C-amido, and guanyl;

and wherein said acyl compound has the structure set forth in formula 3

(3) 

wherein
A is selected from the group consisting of nitrogen, oxygen and sulfur and it is understood that when A is oxygen or sulfur, R^3 does not exist and there is no bond;

B is selected from the group consisting of carbon and nitrogen and it is understood that when B is nitrogen, R^6 does not exist and there is no bond;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and halogen;

when A is nitrogen,

R^3 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl;

R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino and $-NR^{12}R^{13}$, wherein

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

R^4 and R^5 or R^5 and R^6 may combine to form a six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring.

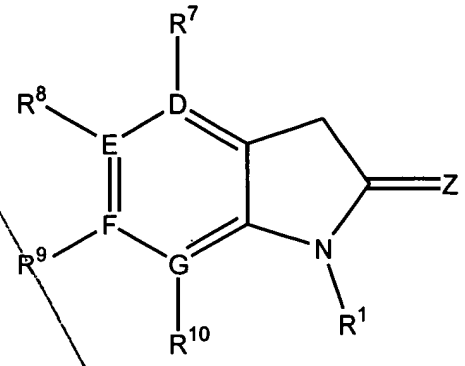
39. The combinatorial library of claim 38, wherein said azaindolin-2-one is selected from the group consisting of the indole portion of the compounds listed in Table 1.

40. The combinatorial library of claim 38, wherein said acyl compound is selected from the group consisting of the acyl portion of the compounds listed in Table 1.

41. A method for synthesizing an indolinone compound of

any one of claims 1-17 comprising the step of reacting a first reactant with a second reactant in a solvent and in the presence of a base at elevated temperatures, wherein said first reactant is an azaindolin-2-one having the structure set forth in formula 2

(2)



wherein

D, E, F and G are independently selected from the group consisting of carbon and nitrogen but at least one of D, E, F and G must be nitrogen and it is understood that when D, E, F or G is nitrogen, R^7, R^8, R^9 and R^{10}, respectively, do not exist and there is no bond;

R^7, R^8, R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino, and $-NR^{12}R^{13}$, wherein

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

cont'd C6

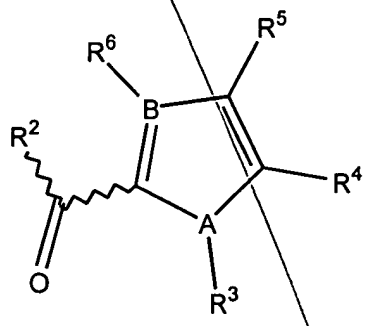
Z is selected from the group consisting of oxygen, sulfur and NR^{11} wherein,

R^{11} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl; and

R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, trihalomethanecarbonyl, sulfonyl, trihalomethanesulfonyl, C-carboxyl, O-carboxyl, C-amido, and guanyl;

and wherein said second reactant is an acyl compound having the structure set forth in formula 3

(3)



wherein

A is selected from the group consisting of nitrogen, oxygen and sulfur and it is understood that when A is oxygen or sulfur, R^3 does not exist and there is no bond;

B is selected from the group consisting of carbon and nitrogen and it is understood that when B is nitrogen, R^6 does not exist and there is no bond;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and halogen;

when A is nitrogen,

R^3 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl;

R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino and $-NR^{12}R^{13}$, wherein

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

R^4 and R^5 or R^5 and R^6 may combine to form a six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring.

42. The method of claim 41, wherein said first reactant is an azaindolin-2-one selected from the group consisting of the indole portion of the compounds listed in Table 1.

43. The method of claim 41, wherein said second reactant is an acyl compound selected from the group consisting of the acyl portion of the compounds listed in Table 1.

44. The method of claim 41, wherein said base is selected from the group consisting of a nitrogen base and an inorganic

base.

45. The method of claim 41, wherein said solvent is selected from the group consisting of water, an alcohol, and dimethylformamide.

Add C8

add D5